Claims

1. A peptide, which is a sequence variant and a functional and/or structural mimic of peptide YY, said peptide comprising at least one modification of the amino acid sequence set forth in SEQ ID NO: 2 (h-PYY 3-36), wherein said peptide

- includes a modification that conformationally constrains the relative position of the N-terminal amino acid of that part of SEQ ID NO 2 present in the peptide and amino acid 34 of SEQ ID NO: 2 in the peptide; and/or
- includes a branched amino acid sequence resulting in 2 free N-terminal amino acids; and/or
- includes N-terminal and/or C-terminal addition of a net basic amino acid sequence;
- optionally further includes deletion of amino acids 1-5 of SEQ ID NO: 2; and/or
- includes deletion of any one or more of amino acid residues 8-15 of SEQ ID NO: 2 without deletion of all of amino acids 1-7 of SEQ ID NO 2; and/or
- includes deletion of amino acids 6 and 7 of SEQ ID NO: 2 without deletion of all of amino acids 1-5 of SEQ ID NO 2; and/or
- includes deletion of amino acids 16-19 of SEQ ID NO: 2 without deletion of all of amino acids 1-15 of SEQ ID NO 2; and/or
- includes two cross linkable protected Cys amino acid substitutions;

wherein said peptide further comprises at most 6 substitutions in the amino acid sequence set forth in SEQ ID NO: 2 , each of which is a structure and/or functionality preserving substitution.

2. The peptide according to claim 1, wherein the modification that conformationally constrains the relative position of amino acids 1 and 34 of SEQ ID NO: 2 is selected from the group consisting of introduction of a disulfide bridge, introduction of a rigid bend involving positions corresponding to residues 9 and 10 in SEQ ID NO: 2, and introduction of at least one stabilising amide bond between amino acid side chains.

3. A peptide of formula I

R^1-X-Y-Z-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-R^2

(I)

wherein

A^{22} is Ala or a structure and/or functionality preserving substitution thereof;
A^{23} is Ser or a structure and/or functionality preserving substitution thereof;
A^{24} is Leu or a structure and/or functionality preserving substitution thereof, His or Cys;
A^{25} is Arg or a structure and/or functionality preserving substitution thereof;
A^{26} is Leu or a structure and/or functionality preserving substitution thereof, His or Cys;
A^{27} is Tyr or a structure and/or functionality preserving substitution thereof;
A^{28} is Leu or a structure and/or functionality preserving substitution thereof, or Cys;
A^{29} is Asn or a structure and/or functionality preserving substitution thereof, or Lys which is optionally coupled to an amino acid sequence via a peptide bond at the ε-amino group;
A^{30} is Leu or a structure and/or functionality preserving substitution thereof;
A^{31} is Val or a structure and/or functionality preserving substitution thereof, or Cys;
A^{32} is Thr or a structure and/or functionality preserving substitution thereof;
A^{33} is Arg or a structure and/or functionality preserving substitution thereof;
A^{34} is Gln or a structure and/or functionality preserving substitution thereof;
A^{35} is Arg or a structure and/or functionality preserving substitution thereof; and
A^{36} is Tyr or a structure and/or functionality preserving substitution thereof;

Z is a peptide of formula

A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}

which is absent or wherein,

A^{13} is Ser or a structure and/or functionality preserving substitution thereof or absent;

A^{14} is Pro or a structure and/or functionality preserving substitution thereof or absent;

A^{15} is Glu or a structure and/or functionality preserving substitution thereof or absent;

A^{16} is Glu or a structure and/or functionality preserving substitution thereof or absent;

A^{17} is Leu or a structure and/or functionality preserving substitution thereof or absent;

A^{18} is Asn or a structure and/or functionality preserving substitution thereof;

A^{19} is Arg or a structure and/or functionality preserving substitution thereof;

A^{20} is Tyr or a structure and/or functionality preserving substitution thereof; and

A^{21} is Tyr or a structure and/or functionality preserving substitution thereof;

Y is a peptide of formula

A^8-A^9-A^{10}-A-B

which is absent or wherein

A^8 is Pro or a structure and/or functionality preserving substitution thereof;

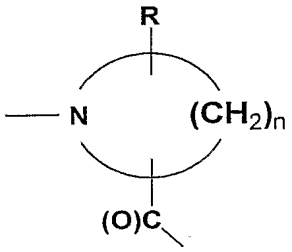
A^9 is Gly or a structure and/or functionality preserving substitution thereof;

A^{10} is Glu or a structure and/or functionality preserving substitution thereof, or absent; and

A-B designates a dipeptide A^{11}-A^{12} selected from the group consisting of Gly-Gly, Pro-Gly, Gly-Pro, Sar-Sar, Sar-Hyp, Hyp-Sar, Pro-Sar, Sar-Pro, Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp, where Pro and Hyp independently may be an L or D form, where the ring structure of Pro and Hyp is optionally substituted with halogen, nitro, methyl, amino, or phenyl, Hyp represents 3-hydroxyproline or 4-hydroxyproline, Sar represents sarcosine, or one or both of the amino acid residues of A-B is a Sar,

or an N-cyclohexylglycine residue, or

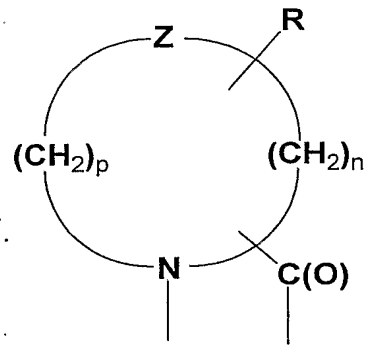
A and B each independently represents a group of the formula II



(II)

wherein n is an integer having the value 3, 4, or 5, and R represents an optional substituent, preferably selected from the group consisting of halogen, phenyl, hydroxy, NH_2, and C(1-6)alkyl optionally substituted with halogen, or

A-B designates the formula IIa



(IIa)

wherein n is an integer having the value 0, 1, 2, and 3, p is an integer having the value 0, 1, 2, and 3, Z represents O or S, and R represents an optional substituent, preferably selected from the group consisting of halogen, phenyl, hydroxy, NH_2, and C(1-6)alkyl, or

A and B independently represents an amino acid residue having a saturated carbocyclic structure of 4, 5 or 6 members and where in said carbocyclic structure further comprises one or more heteroatoms,

X is a peptide of formula

A^3-A^4-A^5-A^6-A^7

which is absent or wherein

A^3 is Ile or a structure and/or functionality preserving substitution thereof, or Cys;

A^4 is Lys or a structure and/or functionality preserving substitution thereof;
A^5 is Pro or a structure and/or functionality preserving substitution thereof, or Cys;
A^6 is Glu or a structure and/or functionality preserving substitution thereof; and
A^7 is Ala or a structure and/or functionality preserving substitution thereof, or Cys;

R^1 is absent or an amino acid sequence; and
R^2 is absent or an amino acid sequence;

wherein said peptide comprises at most one disulfide bridge selected from Cys^3-S-S-Cys^{31}, Cys^3-S-S-Cys^{28}, Cys^5-S-S-Cys^{26}, and Cys^7-S-S-Cys^{24};

or wherein A is absent, Asp or a structure and/or functionality preserving substitution thereof and B is absent, Ala or a structure and/or functionality preserving substitution thereof and said peptide comprises a disulfide bridge selected from Cys^3-S-S-Cys^{31}, Cys^3-S-S-Cys^{28}, Cys^5-S-S-Cys^{26}, and Cys^7-S-S-Cys^{24};

wherein the number of structure and/or functionality preserving substitutions does not exceed 6;
wherein the C-terminal amino exposes a free carboxylic acid group or an amide group; and

or a multimer and/or pharmaceutically acceptable salt thereof.

4. The peptide according to any one of claims 1-3, which binds to receptor Y2.

5. The peptide according to any one of claims 1-4, which binds with higher affinity to receptor Y2 than to receptor Y1.

6. The peptide according to claim 5, wherein the ratio between affinities for receptor Y2 and receptor Y1 is at least 10, such as at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, and at least 100.

7. The peptide according to claim 5 or 6, wherein the ratio between affinities for receptor Y2 and receptor Y1 is at most 200, such as at most 190, at most 180, at

most 170, at most 160, at most 150, at most 140, at most 130, at most 120, and at most 110.

8. The peptide according to any one of the preceding claims, which has an EC50 < 1 nM in the efficacy assay set forth in Example 2.

9. The peptide according to any one of the preceding claims, which has an IC50 < 1 nM in the Y2-binding assay set forth in Example 2.

10. The peptide according to any one of the preceding claims which binds to receptor Y5.

11. The peptide according to claim 10, which binds with higher affinity to receptor Y5 than to receptor Y1.

12. The peptide according to claim 11, wherein the ratio between affinities for receptor Y5 and receptor Y1 is at least 10, such as at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, and at least 100.

13. The peptide according to claim 12, wherein the ratio between affinities for receptor Y5 and receptor Y1 is at most 200, such as at most 190, at most 180, at most 170, at most 160, at most 150, at most 140, at most 130, at most 120, and at most 110.

14. The peptide according to any one of the preceding claims, which has an IC50 < 1 nM in the Y5-binding assay set forth in Example 3.

15. The peptide according to any one of the preceding claims, which has an IC50 and/or EC50 value which is at least 40% of that of the peptide having the amino acid sequence set forth in SEQ ID NO: 2, such as at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 110%, at least 120%, at least 130%, at least 140%, and at least 150% of the IC50 and or EC50 value of the peptide having the amino acid sequence set forth in SEQ ID NO: 2, when the IC50 and/or EC50 values are measured in the assays set forth in Example 2.

16. The peptide according to any one of the preceding claims, which has an IC50 value which is at least 40% of that of the peptide having the amino acid sequence set forth in SEQ ID NO: 2, such as at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 110%, at least 120%, at least 130%, at least 140%, and at least 150% of the IC50 value of the peptide having the amino acid sequence set forth in SEQ ID NO: 2, when the IC50 value is measured in the assay set forth in Example 3.

17. The peptide according to any one of the preceding claims which is a structural and/or functional mimic of the peptide having the amino acid sequence set forth in SEQ ID NO: 2.

18. The peptide according to any one of claims 3-17, insofar as these are dependent on claim 3, wherein structure or functionality preserving substitutions include exchange between
any of Ala, Cys, Ser, and Thr;
Asp and Glu;
any of Asn, Gln, and His;
any of Arg, Lys, Ornithin, Dab (1,4 diaminobutyric acid), and Dapa (1,3 diaminopropionic acid);
any of Ile, Leu, Met, Val Nle (Norleucine), and Nva (Norvaline);
any of Phe, Tyr, and Trp; and
Gly and Pro.

19. The peptide according to any one of claims 3-18, insofar as these are dependent on claim 3, wherein A^{29} is Lys.

20. The peptide according to claim 19, wherein Lys^{29} is coupled to an amino acid sequence via a peptide bond at the ε-amino group.

21. The peptide according to claim 20, wherein Lys^{29} is coupled to SEQ ID NO: 23 via a peptide bond at the ε-amino group.

22. The peptide according to any one of claims 3-21, insofar as these are dependent on claim 3, wherein at most one of A^{24}, A^{26}, A^{28}, and A^{31} is Cys.

23. The peptide according to any one of claims 3-22, insofar as these are dependent on claim 3, comprising the disulfide bridge Cys^3-S-S-Cys^{31}.

24. The peptide according to any one of claims 3-22, insofar as these are dependent on claim 3, comprising the disulfide bridge Cys^3-S-S-Cys^{28}.

25. The peptide according to any one of claims 3-22, insofar as these are dependent on claim 3, comprising the disulfide bridge Cys^5-S-S-Cys^{26}.

26. The peptide according to any one of claims 3-22, insofar as these are dependent on claim 3, comprising the disulfide bridge Cys^7-S-S-Cys^{24}.

27. The peptide according to any one of claims 3-22 insofar as these are dependent on claim 3, wherein X has the amino acid sequence set forth in SEQ ID NO: 23.

28. The peptide according to any one of claims 3-22, insofar as these are dependent on claim 3, wherein X is absent.

29. The peptide according to any one claims 3-28, insofar as these are dependent on claim 3, wherein A and B, independently are selected from the group consisting of N- and C(O)- radicals of the following compounds:
D/L-azetidin-3-carboxylic acid,
D/L-azetidin-2-carboxylic acid,
D/L-Indolin-2-carboxylic acid,
D/L-1,3-dihydro-isoindol-1-carboxylic acid,
D/L-thiazolidin-4-carboxylic acid,
D/L-pipecolinic acid,
D/L-nipecotinic acid,
isonipecotinic acid,
L/D-2-carboxymorpholin,
L/D-1,2,3,4-tetrahydroquinolin-3-carboxylic acid,

L/D-1,2,3,4-tetrahydroquinolin-3-carboxylic acid, and
4-carboxy-4-phenyl-piperidin.

30. The peptide according to any one of claims 3-28, insofar as these are dependent on claim 3, wherein A-B designates 4-(2-aminoethyl)-6-dibenzofuranpropionic acid.

31. The peptide according to any one of claims 3-29, wherein A-B is a dipeptide.

32. The peptide according to claim 31, wherein A and B both designate Pro or a derivative thereof.

33. The peptide according to claim 32, wherein Pro or its derivative, independently, is an L or D form.

34. The peptide according to claim 32, wherein the derivative of Prolin has one or more substituents in the 3, 4 or 5 position, said substituents being selected from hydroxy, amino and phenyl.

35. The peptide according to any one of claims 3-28, insofar as these are dependent on claim 3, wherein A and B independently represents an amino acid residue having a saturated carbocyclic structure of 4, 5 or 6 members, wherein said carbocyclic structure further comprises one or more heteroatoms selected from the group consisting of N, O and S.

36. The peptide according to any one of claims 3-28, insofar as these are dependent on claim 3, wherein B, A^{13}, A^{14}, A^{15}, and A^{16} are absent.

37. The peptide according to claim 36, wherein A^{10}, A, and A^{17} are present.

38. The peptide according to claim 3-28, insofar as these are dependent on claim 3, wherein A^{10}, A, B, A^{13}, A^{14}, A^{15}, A^{16}, and A^{17} are absent.

39. The peptide according to any one of claims 36-38, wherein A^{8}, A^{9}, A^{18}, A^{19}, A^{20}, and A^{21} are present.

40. The peptide according to any one of claims 3-28, insofar as these are dependent on claim 3, wherein Y is present.

41. The peptide according to any one of claims 3-28, insofar as these are dependent on claim 3, wherein Y is absent.

42. The peptide according to any one of claims 3-28, 40 and 41, insofar as these are dependent on claim 3, wherein Z is present.

43. The peptide according to any one of claims 3-28, 40 and 41, insofar as these are dependent on claim 3, wherein Z is absent.

44. The peptide according to claim 3-21, insofar as these are dependent on claim 3, wherein X is absent and Y and Z are present.

45. The peptide according to any one of claims 3-44, insofar as these are dependent on claim 3, wherein R^1 designates an amino acid sequence having between 4 and 20 amino acid residues.

46. The peptide according to claim 45, where R^1 designates an amino acid sequence of 6 amino acid residues.

47. The peptide according to claim 45-46, wherein the amino acid residues in R^1 are basic.

48. The peptide according to claim 47, wherein the amino acid residues in R^1 are selected from Lys, Arg, His, and Orn.

49. The peptide according to claim 48, wherein R^1 consists of six Lys residues.

50. The peptide according to any one claims 3-49, insofar as these are dependent on claim 3, wherein R^2 is an amino acid sequence having between 4 and 20 amino acid residues.

51. The peptide according to claim 50, where R^2 is an amino acid sequence of 6 amino acid residues.

52. The peptide according to claim 50-51, wherein the amino acid residues in R^2 are basic.

53. The peptide according to claim 52, wherein the amino acid residues in R^2 are selected from Lys, Arg, His, and Orn.

54. The peptide according to claim 53, wherein R^2 consists of six Lys residues.

55. The peptide according to any one of claims 3-44, insofar as these are dependent on claim 3, wherein R^1 designates acylation of X with an optionally substituted straight, branched, saturated, unsaturated, or aromatic C(1-22)carboxylic acid where the substitutent is selected from hydroxy, halogen, C(1-6)alkyl, nitro or cyano and may be situated on the carbon chain or the aromatic moiety.

56. The peptide according to claim 55, wherein said C(1-22)carboxylic acid is a C(1-7)carboxylic acid selected from the group consisting of acetic acid, propionic acid, butyric acid and isomers thereof, and benzoic acid.

57. The peptide according to claim 3 which has the structure set forth in any one of SEQ ID NOs.: 3-22.

58. The peptide according to any one of the preceding claims, which is in the form of a dimer comprising two copies of the peptide according to any one of the preceding claims.

59. A method for the preparation of the peptide according to any one of the preceding claims, which comprises
a) synthesizing the peptide by means of solid phase or liquid phase peptide synthesis and recovering the synthetic peptide thus obtained; or
b) when the peptide is constituted by naturally occurring amino acids, expressing a nucleic acid construct that encodes the peptide in a host cell and recovering the

expression product from the host cell culture; or

c) when the peptide is constituted by naturally occurring amino acids, effecting cell-free *in vitro* expression of a nucleic acid construct that encodes the peptide and recovering the expression product; or

d) combining the methods of a, b, and c to obtain fragments of the peptide, subsequently ligating the fragments to obtain the peptide, and recovering the peptide.

60. A pharmaceutical composition comprising, as an active principle, a peptide according to any one of claims 1-58 in admixture with a pharmaceutically acceptable carrier, diluent, vehicle or excipient.

61. The pharmaceutical composition according to claim 60, which in a dose form selected from the group consisting of an oral dosage form, a buccal dosage form, a sublingual dosage form, an anal dosage form, and a parenteral dosage form such as an intraveneous, an intraarterial, an intraperitoneal, a subdermal, an intradermal or an intracranial dosage form.

62. A pharmaceutical composition according to claim 60 or 61, which provides sustained release of the peptide.

63. A method for reducing body weight in a subject, the method comprising administering, to the subject, an effective amount of the peptide according to any one of claims 1-58, or a pharmaceutical composition according to any one of claims 60-62.

64. A method for enhancing body weight in a subject, the method comprising administering, to the subject, an effective amount of the peptide according to any one of claims 1-58, or a pharmaceutical composition according to any one of claims 60-62.

65. The method according to claim 63 or 64, wherein administration is via a route selected from the group consisting of the parenteral route such as the intradermal, the subdermal, the intraarterial, the intravenous, and the intramuscular route; the

peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

66. The method according to any one of claims 63-65 wherein the effective amount of the peptide is at least about 10 μg/kg body weight/day, such as at least 100 μg/kg body weight/day, at least 300 μg/body weight/day, and at least 1000 μg/kg body weight/day.

67. The method according to any one of claims 63-66 wherein the effective amount of the peptide is at most about 100 mg/kg body weight/day, such as at most 50 mg/kg body weight/day and at most 10 mg/kg body weight/day.

68. The method according to any one of claims 63-67, wherein the effective amount of the peptide is about 100 μg/kg body weight/day.

69. The method according to any one of claims 63-67, wherein the effective amount of the peptide is about 300 μg/kg body weight/day.

70. The method according to any one of claims 63-67, wherein the effective amount of the peptide is about 1000 μg/kg body weight/day.

71. The method according to any one of claims 63 and 65-70, insofar as these depend on claim 63, which is used to treat or ameliorate conditions characterised by excessive body fat deposition.

72. The method according to any one of claims 64 and 65-70, insofar as these depend on claim 64, which is used to treat or ameliorate conditions characterised by reduced body fat deposition.

73. The peptide according to any one of claims 1-58 for use as a pharmaceutical.

74. Use of the peptide according to any one of claims 1-58 for the preparation of a pharmaceutical composition for the treatment or amelioration of conditions characterized by excess body fat deposition.

75. Use of the peptide according to any one of claims 1-58 for the preparation of a pharmaceutical composition for the treatment or amelioration of conditions characterized by reduced body fat deposition.

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